

### REMARKS

Applicant thanks Examiner Pak for his thorough analysis of the application. In response to the Office Action mailed October 2, 2002, the application has been carefully reviewed and amended. Entry of the foregoing amendments and reconsideration of the application is respectfully requested.

#### Allowable Subject Matter

The combination of NAD<sup>+</sup> and vanadyl sulfate, with proper language correction has been deemed allowable. [Paper 2, Page 4]

#### *Claims 42-78*

Claims 42-78 recite in part a composition comprising "NAD<sup>+</sup> and one of (i) vanadyl sulfate and (ii) a vanadyl sulfate complex.

As set forth in Paper 2, Page 4, the combination of NAD<sup>+</sup> with vanadyl sulfate, (with the proper language correction as noted for Claim 1) was deemed to be allowable. Therefore, applicant respectfully submits independent Claim 42 and depending Claims 43-78 are in condition for allowance.

#### Claim Objections

##### *Claims 37-39*

Claims 37-39 stand objected to under 37 CFR §1.75, as being substantial duplicates of Claims 1-3.

Claims 37-39 have been cancelled, thereby removing the basis of the objection under 37 CFR §1.75.

#### Rejections Under 35 USC §112

Claims 1-39 stand rejected under 35 USC §112, second paragraph. Claims 1-36 have been amended to recite a proper and definite Markush group. Thus, the rejection of these claims under 35 USC §112 is believed to have been overcome.

Claim 3 has been amended to provide the omitted right parentheses.

Rejections Under 35 USC §102*Claims 1-3*

Claims 1-3 stand rejected under 35 USC §102(b) as being anticipated by or, in the alternative, under 35 USC §103(a) as obvious over Vadgama, et al. (WO 98/20332). The examiner relies upon Vadgama to disclose a solution mixture that contains potassium ferricyanide and NAD<sup>+</sup>, citing examples two and three on pages 9-10.

Vadgama is directed to a bio sensor having an enzyme layer and an outer diffusion limiting barrier membrane wherein detectors are located on opposing sides of the enzyme layer and the diffusion limiting barrier membrane. The enzyme layer incorporates an enzyme capable of interacting with a selected analyte.

Vadgama impregnates the enzyme laminate with *lactate* dehydrogenase and NAD<sup>+</sup>. Alternatively, the enzyme laminate is fabricated with *malate* dehydrogenase and NAD<sup>+</sup>. (Page 9-10)

These chemicals are selected to provide an electrochemical means preferably of the non potentiometric, wherein amperometric detection is preferred. (Vadgama, Page 6)

As amended, Claim 1 recites in part "NAD<sup>+</sup> and at least one of a species including at least one of a multivalent transition metal ion complex thereof, the species being in a state selected to accelerate in vivo oxidation of alcohol in the *absence* of a dehydrogenase. [emphasis added]

As expressly set forth in Vadgama, each of the enzyme laminate fabrications employs either lactate dehydrogenase or malate dehydrogenase, and does not disclose the acceleration of in vivo oxidation of alcohol in the absence of a dehydrogenase.

Applicant respectfully submits that Claim 1 distinguishes Vadgama. As Claims 2 and 3 depend from Claim 1 and include all limitations thereof, applicant respectfully submits these claims are also in condition for allowance.

*Claims 1-2, 4-11, 15, 17-19, 22-23, 34-35, 37-38*

Claims 1-2, 4-11, 15, 17-19, 22-23, 34-35, 37-38 stand rejected under 35 U.S.C. §102(b) as anticipated by, or in the alternative, under 35 U.S.C. §103 as obvious over Blass (U.S. Patent No. 5,053,396). (Paper 2, Page 6)

Examiner Pak relies upon Col. 5, Lines 37-61 to disclose the recited constituents.

The components as indicated are mixed together and formulated to the desired therapeutic compositions in a manner well known in the art.

Preferred and minimum dosages for the components to be included within the composition (per dose) are indicated below without limiting the invention.

Component	Preferred dosage	Range	
Acetylsalicylic acid	600-900 mg	300-1000 mg	40
or Ibuprofen	150-300 mg	100-300 mg	
or Fenoprofen calcium	300-600 mg	200-800 mg	
Nicotinamide	300-300 mg	70-1500 mg	
NAD	100-200 mg	70-300 mg	45
Pantothenic acid	100-400 mg	50-300 mg	
Riboflavin	30-60 mg	5-100 mg	
Pyridoxine HCl	30-60 mg	5-100 mg	
Thiamine HCl	70-150 mg	50-600 mg	
Ascorbic acid	250-300 mg	100-800 mg	
Fructose	5000 mg	2000-15000 mg	50
Promethazine HCl	25 mg	10-50 mg	
or Chlorpheniramine	4 mg	2-6 mg	
malate	—	0-4000 mg	
Sodium bicarbonate	—	0-4000 mg	55
Potassium bicarbonate	—	0-4000 mg	
Magnesium carbonate	—	0-4000 mg	
or Magnesium oxide or hydroxide	—	0-4000 mg	
Calcium carbonate	—	0-4000 mg	60
Citric acid	1200-1800 mg	0-4000 mg	
Zinc ions	1.5 mg	0.5-20 mg	
Iron ions	10 mg	5-30 mg	
Manganese ions	0.6 mg	0.3-1.0 mg	60
Chromium ions	1 mcg	1 mcg	
Sweetening or flavouring agents and other additives	as required		

Any of the metals mentioned in this specification could be present wholly or partly as the salts of gluconic, levulinic, ascorbic, citric or phosphoric acids, or any other suitable acids, where this would be advantageous. They could also be present wholly or partly as amino acid chelates.

However, applicant respectfully submits, as described herein and supported by the attached search results of Attachment A and B, Blass does not disclose the recited multivalent transition metal ions, or complexes thereof.

Specifically, the recited zinc and manganese ions in Blass are a one valent state metal and thus are not a multivalent transition metal ion. Therefore, the recited zinc and manganese ions in Blass cannot act as a catalyst in the redox reaction.

With respect to the recited iron ions and chromium ions, applicant notes and has set forth in the accompanying search results as Attachment A, that the addition of the recited ascorbic acid in Blass would reduce both these metals to a reduced state, and would not exist in the recited ion or complex ion state.

Therefore, applicant respectfully submits as amended, Claim 1 distinguishes over Blass.

As Claims 2, 4-11, 15, 17-19, 22-23 and 34-35 depend from Claim 1 and include all limitations thereof, applicant respectfully submits these claims are also in condition for allowance.

#### Newly Added Claims

##### *Claims 79-110*


Newly added Claims 79-110 recite in part "a composition for accelerating in vivo oxidation of alcohol, the composition comprising  $\text{NAD}^+$  in one of acetaldehyde dehydrogenase and alcohol dehydrogenase.

As none of the references of record disclose or suggest use of acetaldehyde dehydrogenase or alcohol dehydrogenase in combination with  $\text{NAD}^+$ , nor a combination for accelerating in vivo oxidation of alcohol, applicant respectfully submits independent Claims 79 is in condition for allowance.

As Claims 80-110 depend from Claim 79 and include all limitations thereof, these claims are also believed in condition for allowance.

Therefore, applicant respectfully submits all the pending claims, Claims 1-36 and 42-110 are in condition for allowance. If, however, the examiner feels that any further issues remain, he is cordially invited to contact the undersigned so that such matters may be promptly resolved.

Respectfully submitted,

  
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Brian G. Shaw, Registration No. 33,782  
HARTER, SECREST & EMERY LLP  
1600 Bausch & Lomb Place  
Rochester, New York 14604

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## Appendix A

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- ☐ **61. Inhibition of mammalian 5-lipoxygenase and cyclooxygenase by flavonoids and phenolic dietary additives. Relationship to...**  
**M J Loughton / P J Evans / M A Moroney / J R Houlst / B Halliwell, *Biochem Pharmacol*, Oct 1991**  
 ...degradation caused by the antibiotic bleomycin in the presence of ferric ions. These compounds...possibly caused by changing relative contributions of ability to reduce ferric-bleomycin or to chelate iron ions from the bleomycin...

MEDLINE Citation on **BioMedNet**  
MEDLINE[similar results](#)

- ☐ **62. 3-O-alkylascorbic acids as free radical quenchers. II. Inhibitory effects on some lipid peroxidation models.**  
**Y Nihro / S Sogawa / T Sudo / T Miki / H Matsumoto / T Satoh, *Chem Pharm Bull (Tokyo)*, Jul 1991**  
 ...dodecylcarbamethylascorbic acid (3-RASA,3,HX-0112...lesions induced by ischemia-reperfusion...examined the mode of action of 3-RASA...produced) against ferric ions and superoxide...chain-reaction of the peroxidation induced by Fe(2+)-linoleic acid hydroxyperoxide...

MEDLINE Citation on **BioMedNet**  
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- ☐ **3. Oxidation of lipids and membranes I: in vitro formation of peroxidative lipid polymers.**  
**M Wolman, *J Supramol Struct*, Feb 1975**

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...polym rs-w re-obtained by oxidizing partly-emulsified linolenic acid with different oxidants. The speed of formation of polymers...In the absence of albumen. With different...xidation with ferric ions, with K-dichromate...delay was caused by some retarders...

# **MEDLINE Citation on BioMedNet**

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- 64. Benzohydroxamic acid as a reductometric titrant: Determination of manganese, chromium and vanadium in steels  
**Ahmed, M.K. / Subbarao, C., Talanta, Jan 1981**  
 A method has been developed for the rapid determination of manganese and chromium by direct stepwise reductometric titration with benzohydroxamic acid, and of vanadium by titration with ascorbic acid (with benzohydroxamic acid as indicator)...

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- 65. Subject index  
*Journal of Electroanalytical Chemistry*, Aug 1989  
 91 A Absolute electrode potential The absolute electrode potential: an explanatory note 209(1986)417 Absorption spectroscopy The role of intramolecular association in the electrochemical reduction of viologen dimers and trimers 243(1988)143 Acetaldehyde...

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- 66. Steady state photocurrents associated with electron transfer through planar lipid bilayers by zinc 5,10,15,20....  
**Blenvenue, E. / Seta, P. / Hofmanova, A. / Gavach, C. / Momenteau, M., Journal of Electroanalytical Chemistry, Mar 1984**  
 Bilayer phosphatidylserine membranes sensitized by zinc tetraphenylporphyrin (ZnTPP) and its 1-CH<sup>2</sup>)<sup>2</sup> CO<sup>2</sup>H derivative (ZnTPP-Ac) are formed between one oxidant (Fe<sup>3+</sup>) and one reductant (ascorbic acid) solution. Under visible light...

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- 67. Subject index  
*Journal of Chromatography A*, Jan 1983  
 281 SUBJECT INDEX VOLUMES 151--250 A Absolute configuration Effect of the absolute configuration of cobalt(III) complexes on their chromatographic behaviour 249(1982)65 Absorbance index Abate Numerical spectroscopy: absorbance Index Determination of Abate...

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- 68. Membrane photobiophysics and photochemistry  
**Ti Tien, H., Progress in Surface Science, Jan 1989**

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
Life, as we know it, depends on solar energy, in particular in the visible range of the solar spectrum. However, visible light alone is useless to the living organism unless a means is available for its capture, transformation, and...

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69. Coordination and redox chemistry of some macromolecular systems  
**Skorobogaty, A. / Smith, T.D.,** *Coordination Chemistry Reviews*, Jan 1984  
Coordination Chemistry Reviews, 53 (1984) 55-226  
Elsevier Science Publishers B.V., Amsterdam -Printed in The Netherlands  
**COORDINATION AND REDOX CHEMISTRY OF SOME MACROMOLECULAR SYSTEMS**  
**ANDREW SKOROBOGATY and THOMAS D. SMITH**  
Chemistry Department, Monash...

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70. The process involved in the binding of technetium-99m to human serum albumin  
**Williams, M.J. / Deegan, T.,** *The International Journal Of Applied Radiation And Isotopes*, Dec 1971  
Pertechnetat wurde reduziert zu dem funfwertigen Zustande durch Verdampfung bis trocken in vacuo einer Losung in verdunnter HCl. Eine Behandlung des trockenen Niederschlags mit 5 ml von 3% menschlichem Serumalbumin mit 10 mg Vitamin C, mit...

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- ☐ **171.** Reductive metabolism of ascorbic acid in the central nervous system.

**D D Pietronigro / M Hovsepian / H B Demopoulos / E S Flamm, *Brain Res*, Apr 1985**

...as monitored by both ascorbyl radical-dependent **nicotinamide adenine dinucleotide (NADH)** oxidase...and paralleled **ascorbic acid** levels. Subcellular fractionation of rat cerebrum...regeneration of reduced **ascorbic acid** in the central...

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- ☐ **172.** Inhibition of radical adduct reduction and reoxidation of the corresponding hydroxylamines in vivo spin trapping of...

**M Sentjurs / R P Mason, *Free Radic Biol Med*, Feb 1992**

...metabolic inhibitors of nitroxide reduction were tested...is metabolized by liver to .CCl3...glutathione (GSH) nor **ascorbic acid** occurred ex vivo...the presence of NEM faster re...and reduced **nicotinamide adenine dinucleotide phosphate (NADPH)**...

MEDLINE Citation on **BioMedNet**

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- ☐ **173.** Ascorbic acid potentiates the substrate-specific inhibition of mixed-function oxidation and the stimulation of NADPH...

**M R Montgomery / P B Shamblin, *J Toxicol Environ Health*, Feb 1984**

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...stimulated the hepatic-microsomal-oxidation- f  
**nicotinamide ad nine dinucleotide phosphate**  
(NADPH) equally in the absence f...activity was  
precluded by the rapid nonenzymatic **reduction of**  
cytochrome c by ascorbate. The paraquat-ascorbate  
redox couple...

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- ▮ 174. Photosensitization with anticancer agents 14.  
Perylenequinonoid pigments as new potential  
photodynamic therapeutic...  
**Diwu, Z. / Lown, J.W., Journal of Photochemistry and  
Photobiology A: Chemistry, Dec 1992**  
When perylenequinonoid pigments were irradiated with  
visible light, semiquinone radicals, singlet oxygen,  
superoxide anion radical, hydroxyl radical and hydrogen  
peroxide were detected. The formation of the  
semiquinone radicals and...

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- ▮ 175. Modulation of cytotoxicity of menadione sodium bisulfite  
versus leukemia L1210 by the acid-soluble thiol pool.  
**S A Akman / M Dietrich / R Chlebowski / P  
Limberg / J B Block, Cancer Res, Nov 1985**  
...not by 1 mM ascorbic acid or 180  
microM...concentrations of vitamin K3...generation by  
L1210, maximal...the reduced **nicotinamide adenine  
dinucleotide phosphate**...and total **nicotinamide  
adenine dinucleotide phosphate**...depletion of the  
NADPH...prevented by coincubation...coincubation with  
**ascorbic acid** or alpha...

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- ▮ 176. Metabolism of trinitrobenzene sulfonic acid by the rat  
colon produces reactive oxygen species.  
**M B Grisham / C Volkmer / P Tso / T Yamada,  
Gastroenterology, Aug 1991**  
...0.23 nmol.min-1.mg protein-1. Addition of  
**nicotinamide adenine dinucleotide**, reduced form  
(NADH; 1 mmol/L) to colon...9 nmol.min-1.mg-1.  
Similarly, addition of **nicotinamide adenine  
dinucleotide phosphate**, reduced form (NADPH; 1  
mmol...

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- ▮ 177. Calcium uptake by bovine epididymal spermatozoa is  
regulated by the redox state of the mitochondrial  
pyridine nucleotides.  
**S Vijayaraghavan / A Bhattacharyya / D D  
Hoskins, Biol Reprod, Apr 1989**  
...generate NADH (**nicotinamide adenine**

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**dinucle tide). Previous...regulated by the oxidation state of mit chondrial...generating NAD+ (nicotinamide adenine dinucleotide, oxidized...calcium uptake by digitonin...the presence of succinate...**

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178. The extra-weak chemiluminescence generated during oxidation of some tetracycline antibiotics 1. Autoxidation  
**Kruk, I. / Lichszeld, K. / Michalska, T. / Nizinkiewicz, K. / Wronska, J., Journal of Photochemistry and Photobiology B: Biology, Jul 1992**  
Chemiluminescence (CL) appearing during autoxidation of tetracycline (TC) antibiotics has been studied. The CL spectrum consists of four emission bands with maxima at 520, 585, 640 and 700 nm. The bands at 585, 640 and 700 nm are similar to...

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179. Stopped-flow kinetic studies of the coupled dichlorophenol indophenol-nicotinamide adenine dinucleotide reaction  
**Karayannis, M.I. / Siskos, P.A., Analytica Chimica Acta, Jan 1982**  
The kinetics of the reaction of dichlorophenol indophenol with NADH in the presence of phenazine methosulfate as electron carrier were studied by stopped-flow spectrophotometry, and a rate equation and mechanism are proposed. Experimental...

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180. Microsomal electrodes for reduced nicotinamide adenine dinucleotide and its phosphate, glucose-6-phosphate and ascorbate

**Schubert, F. / Scheller, F. / Kirstein, D., Analytica Chimica Acta, Sep 1982**

Rat liver microsomes have been immobilized in a membrane by gelatin entrapment. The resulting membranes can be attached to an oxygen electrode to provide a sensor for several compounds. NADPH and NADH are determined by utilizing the liver...

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